

We claim:

1. Use of an interleukin-33 (IL-33) antagonist in the manufacture of a medicament for use in combination with an interleukin-4 receptor (IL-4R) antagonist for treating an inflammatory disease or disorder, or at least one symptom associated with the inflammatory disease or disorder, wherein the combination of the IL-33 antagonist and the IL-4R antagonist results in enhanced therapeutic efficacy as compared to the IL-33 antagonist alone or the IL-4R antagonist alone.

2. The use of claim 1, wherein the inflammatory disease or disorder is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), asthma and COPD overlap syndrome (ACOS), atopic dermatitis, an allergic response, chronic bronchitis, emphysema, chronic rhinosinusitis with or without nasal polyps, inflammatory bowel disease, Crohn's disease, ulcerative colitis, hypersensitivity pneumonitis, multiple sclerosis, arthritis (osteoarthritis, rheumatoid arthritis and psoriatic arthritis), allergic rhinitis, fibrosis, eosinophilic esophagitis, vasculitis, urticaria, Churg Strauss syndrome, inflammatory pain and psoriasis, optionally wherein:

(a) the chronic obstructive pulmonary disease (i) is exacerbated by one or more of the following: asthma, a viral disease, a bacterial infection, an exposure to an allergen, an exposure to a chemical or chemical fumes, or an exposure to an environmental irritant or air pollution, or (ii) results from, or is exacerbated in part by cigarette smoke; or

(b) the asthma (i) is exacerbated by one or more of the following: a viral disease, a bacterial infection, an exposure to an allergen, an exposure to a chemical or chemical fumes, or an exposure to an environmental irritant or air pollution, or (ii) is eosinophilic asthma, non-eosinophilic asthma, steroid resistant asthma or steroid sensitive asthma.

3. The use of claim 1 or 2, wherein the IL-33 antagonist and the IL-4R antagonist are for use in combination with one or more additional therapeutic agents

useful for alleviating the inflammatory disease or disorder, or at least one symptom of the inflammatory disease or disorder, optionally wherein the one or more additional therapeutic agents is selected from the group consisting of a non-steroidal anti-inflammatory (NSAID), a corticosteroid, a bronchial dilator, an antihistamine, epinephrine, a decongestant, a thymic stromal lymphopoietin (TSLP) antagonist, an IL-1 antagonist, an IL-8 antagonist, an IL-13 antagonist, a different IL-4 antagonist, an IL-4/IL-13 dual antagonist, an IL-33/IL-13 dual antagonist, an IL-5 antagonist, an IL-6 antagonist, an IL-12/23 antagonist, an IL-22 antagonist, an IL-25 antagonist, an IL-17 antagonist, an IL-31 antagonist, a TNF inhibitor, an IgE inhibitor, a leukotriene inhibitor, an oral PDE4 inhibitor, a methylxanthine, nedocromil sodium, cromolyn sodium, a long-acting beta 2 agonist (LABA), a long acting muscarinic antagonist (LAMA), an inhaled corticosteroid (ICS) and another IL-33 antagonist, and optionally wherein the other IL-33 antagonist is selected from the group consisting of a different antibody to IL-33, a different IL-33 receptor based trap, an ST2 antibody, a soluble ST2 receptor, an antagonist to an IL-33 receptor other than ST2, an IL-1RAcP antagonist, and an antibody that interacts with an IL-33/ST2 complex.

4. Use of an interleukin-33 (IL-33) antagonist in the manufacture of a medicament for use in combination with an interleukin-4 receptor (IL-4R) antagonist for treating a fibrotic disease or disorder, or at least one symptom associated with the fibrotic disease or disorder, wherein the combination of the IL-33 antagonist and the IL-4R antagonist results in enhanced therapeutic efficacy as compared to the IL-33 antagonist alone or the IL-4R antagonist alone.

5. The use of claim 4, wherein the fibrotic disease or disorder is a pulmonary fibrotic disease or disorder, optionally wherein the pulmonary fibrotic disease or disorder is selected from the group consisting of idiopathic pulmonary fibrosis, fibrosis associated with acute lung injury or acute respiratory distress, silicosis, radiation-induced fibrosis, bleomycin-induced pulmonary fibrosis, asbestos-induced pulmonary fibrosis, and bronchiolitis obliterans syndrome.

6. Use of an interleukin-33 (IL-33) antagonist in the manufacture of a medicament for use in combination with an interleukin-4 receptor (IL-4R) antagonist for preventing or reducing the severity of an allergic response in a subject in need thereof, wherein the combination of the IL-33 antagonist and the IL-4R antagonist results in enhanced therapeutic efficacy as compared to the IL-33 antagonist alone or the IL-4R antagonist alone.

7. The use of any one of claims 1, 4, or 6, wherein the enhanced therapeutic efficacy is measured by any one or more of the following parameters:

- a) a reduction in the frequency of one or more of the following: eosinophils, activated B cells, activated CD8 T cells, or CD4/CD8 T cell ratio in a tissue sample, optionally wherein the tissue sample is obtained from the lung, liver, kidney, heart, or whole blood;
- b) a reduction in one or more of the following: interleukin-1 beta (IL-1 β), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-13 (IL-13), monocyte chemoattractant protein-1 (MCP-1), or tumor necrosis factor alpha (TNF α) levels in a tissue sample, optionally wherein the tissue sample is obtained from the lung, liver, kidney, heart, or whole blood; or
- c) a reduction in the gene expression level of one or more of the following: *Il4*, *Il5*, *Il6*, *Il9*, *Il13*, *Il1rl1*, *Il13ra2*, *tnf*, *Tgfb1*, *Ccl2*, *Ccl11*, *Ccl24*, *Col15a1* and/or *Col24a1* in a tissue sample, optionally wherein the tissue sample is obtained from the lung, liver, kidney, heart, or whole blood,

optionally wherein the enhanced therapeutic efficacy is further measured by any one or more of the following parameters:

- a) a reduction in serum IgE levels;
- b) a reduction in goblet cell metaplasia in the lung;
- c) an improvement in lung consolidation; or
- d) a decrease in sub-epithelial fibrosis in the lung.

8. The use of any one of claims 1-7, wherein the combination use of the IL-33 antagonist with the IL-4R antagonist results in an increase in a type 1 immune response, and/or a reduction in a type 2 immune response elicited by the disease, or by the causative agent of the disease or allergy.

9. The use of any one of claims 1-8, wherein the IL-4R antagonist is an antibody or antigen-binding fragment thereof that binds IL-4R α and prevents the interaction of IL-4 and/or IL-13 with a type 1 or type 2 IL-4 α receptor, optionally wherein the antibody or antigen-binding fragment thereof that binds IL-4R α prevents the interaction of IL-4 and/or IL-13 with both type 1 and type 2 IL-4 α receptors.

10. The use of claim 9, wherein the IL-4R α antibody or antigen-binding fragment thereof comprises:

(a) the heavy chain complementarity determining regions (HCDRs) of a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO:335 or 337 and the light chain complementarity determining regions (LCDRs) of a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:336 or 338;

(b) three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 339, the HCDR2 comprises the amino acid sequence of SEQ ID NO:340; the HCDR3 comprises the amino acid sequence of SEQ ID NO:341; the LCDR1 comprises the amino acid sequence of SEQ ID NO:342; the LCDR2 comprises the amino acid sequence of SEQ ID NO:343; and the LCDR3 comprises the amino acid sequence of SEQ ID NO:344;

(c) an HCVR comprising the amino acid sequence of SEQ ID NO: 335 or SEQ ID NO: 337 and an LCVR comprising the amino acid sequence of SEQ ID NO: 336 or SEQ ID NO: 338; or

(d) an HCVR/LCVR amino acid sequence pair of either SEQ ID NOs: 335/336 or SEQ ID NOs: 337/338.

11. The use of any one of claims 1-10, wherein the IL-4R α antagonist is dupilumab or a bioequivalent thereof.

12. The use of any one of claims 1-8, wherein the IL-33 antagonist is an antibody or antigen-binding fragment thereof that binds specifically to IL-33 and blocks the interaction of IL-33 and ST2.

13. The use of any one of claims 1-8, or 12, wherein the antibody or antigen-binding fragment thereof that binds specifically to IL-33:

(a) comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, and 308; and comprises three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, and 316;

(b) comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290 and 308;

(c) comprises a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298 and 316;

(d) comprises (i) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292 and 310, (ii) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294 and 312,

(iii) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296 and 314, (iv) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284 and 318, (v) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286 and 320, and (iv) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288 and 322;

(e) comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: SEQ ID NO: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298 and 308/316;

(f) interacts with an amino acid sequence ranging from about position 1 to about position 12 of SEQ ID NO: 349, and/or with an amino acid sequence ranging from about position 50 to about position 94 of SEQ ID NO: 349 as determined by hydrogen/deuterium exchange;

(g) interacts with an amino acid sequence ranging from about position 112 to about position 123 of SEQ ID NO: 348, and/or with an amino acid sequence ranging from about position 161 to about position 205 of SEQ ID NO: 348 as determined by hydrogen/deuterium exchange;

(h) interacts with either the amino acid sequence of SEQ ID NO: 350, or with the amino acid sequence of SEQ ID NO: 351, or interacts with both SEQ ID NOs: 350 and 351 as determined by hydrogen/deuterium exchange;

(i) comprises the heavy chain complementarity determining regions (HCDRs) and light chain complementarity determining regions (LCDRs) of a heavy chain variable region/light chain variable region (HCVR/LCVR) amino acid sequence pair of SEQ ID NOs: 274/282;

(j) comprises HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 domains, respectively, of SEQ ID NOs: 276-278-280-284-286-288; or

(k) comprises: (a) a heavy chain variable region (HCVR) having the amino acid sequence of SEQ ID NO: 274; and (b) a light chain variable region (LCVR) having the amino acid sequence of SEQ ID NO:282.

14. The use of any one of claims 1-8, 12 or 13, wherein the IL-33 antibody or antigen-binding fragment thereof (a) competes for binding to IL-33 with a reference antibody comprising the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 274/282, or (b) binds to the same epitope on IL-33 as a reference antibody comprising the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 274/282.

15. The use of any one of claims 1-8, wherein the IL-33 antagonist is an IL-33 trap comprising a first IL-33 binding domain (D1) attached to a multimerizing domain (M), wherein D1 comprises an IL-33-binding portion of an ST2 protein, optionally wherein the IL-33 antagonist is an IL-33 trap further comprising a second IL-33 binding domain (D2) attached to D1 and/or M, wherein D2 comprises an extracellular portion of an IL-1RAcP protein.

16. The use of claim 15, wherein:

(a) D1 is attached to the N-terminus of M;

(b) D1 is attached to the C-terminus of M;

(c) D2 is attached to the N-terminus of M;

(d) D2 is attached to the C-terminus of M;

(e) D1 is attached to the N-terminus of D2, and wherein D2 is attached to the N-terminus of M;

(f) D1 comprises the amino acid sequence of SEQ ID NO: 328 or 329, or an amino acid sequence having at least 90% identity thereto;

(g) D2 comprises the amino acid sequence of SEQ ID NO: 330 or 331, or an amino acid sequence having at least 90% identity thereto; or

(h) the IL-33 antagonist is an IL-33 trap comprising a first IL-33 binding domain (D1) attached to a first multimerizing domain (M1), and a second IL-33 binding domain (D2) attached to a second multimerizing domain (M2), wherein the D1 and/or D2 domains comprise an IL-33-binding portion of a receptor selected from the group consisting of ST2 and IL-1RAcP, optionally wherein D1 is attached to the N-terminus of M1, and D2 is attached to the N-terminus of M2.

17. The use of claim 16, wherein the IL-33 antagonist comprises a third IL-33 binding domain (D3) that is attached to either D1 or M1, and wherein D3 comprises an IL-33-binding portion of a receptor selected from the group consisting of ST2 and IL-1RAcP, optionally wherein the IL-33 antagonist comprises a fourth IL-33 binding domain (D4) that is attached to either D2 or M2, and wherein D4 comprises an IL-33-binding portion of a receptor selected from the group consisting of ST2 and IL-1RAcP.

18. The use of claim 17, wherein:

(a) D3 is attached to the N-terminus of D1;
(b) D3 is attached to the C-terminus of M1;
(c) D4 is attached to the N-terminus of D2;
(d) D4 is attached to the C-terminus of M2;
(e) D3 is attached to the N-terminus of D1, and D1 is attached to the N-terminus of M1; and wherein D4 is attached to the N-terminus of D2, and D2 is attached to the N-terminus of M2;

(f) D3 is identical or substantially identical to D4 and wherein D1 is identical or substantially identical to D2; or

(g) D3 and D4 each comprise an IL-33-binding portion of an ST2 protein; and wherein D1 and D2 each comprise an extracellular portion of an IL-1RAcP protein.

19. The use of any one of claims 1-8, wherein the IL-33 antagonist is an IL-33 trap (a) comprising an amino acid sequence selected from the group consisting of

SEQ ID NOs: 323, 324, 325, 326 and 327, or (b) comprising the amino acid sequence of SEQ ID NO: 327.

20. The use of any one of claims 1-19, wherein the IL-33 antagonist and the IL-4R antagonist are:

- (a) are formulated in separate compositions;
- (b) are co-formulated; or
- (c) are formulated for subcutaneous, intravenous, intramuscular, or intranasal use.

21. The use of any one of claims 1-20, wherein the IL-33 antagonist is:

(a) a monoclonal antibody comprising three heavy chain complementarity determining regions (HCDRs) contained within a heavy chain variable region sequence of SEQ ID NO: 274 and three light chain complementarity determining regions (LCDRs) contained within a light chain variable region (LCVR) sequence of SEQ ID NO: 282 and wherein the IL-4R antagonist is a monoclonal antibody comprising three heavy chain complementarity determining regions (HCDRs) contained within a heavy chain variable region sequence of SEQ ID NO: 337 and three light chain complementarity determining regions (LCDRs) contained within a light chain variable region (LCVR) sequence of SEQ ID NO: 338;

(b) a monoclonal antibody comprising the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 274/282 and wherein the IL-4R antagonist is a monoclonal antibody comprising the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 337/338; or

(c) a monoclonal antibody comprising three HCDRs (HCDR1-HCDR2-HCDR3) having the amino acid sequences of SEQ ID NOs: 276-278-280, respectively and three LCDRs (LCDR1-LCDR2-LCDR3) having the amino acid sequences of SEQ ID NOs: 284-286-288, respectively and wherein the IL-4R antagonist is a monoclonal antibody comprising three HCDRs (HCDR1-HCDR2-HCDR3) having the amino acid sequences of SEQ ID NOs: 339-340-341, respectively and three LCDRs (LCDR1-

LCDR2-LCDR3) having the amino acid sequences of SEQ ID NOs: 342-343-344, respectively.

22. The use of any one of claims 1-21, wherein the IL-33 antagonist is REGN3500 and wherein the IL-4R antagonist is dupilumab.